

Claims

1. A pharmaceutical composition comprising:

- i. a microemulsion comprising a lipid core and an amphipathic lipid layer surrounding said lipid core, wherein a hydrophobic portion of said amphipathic lipid layer is associated with said lipid core and a hydrophilic portion of said amphipathic lipid layer is associated with a hydrophilic surface of said amphipathic lipid;
- ii. a bioactive agent; and
- iii. optionally, a lipidized polymer;

10 said bioactive agent being included in said composition in an effective amount, said amphipathic lipid being included in said composition in an amount effective to form a microemulsion with said lipid core, and said lipidized polymer being included in said composition in association with said amphipathic lipid in an amount ranging from about 15 0.01% to about 65% by weight of said composition.

2. The composition according to claim 1 wherein said amphipathic lipid includes an amount of a steroid component effective to increase the stability of said amphipathic lipid.

20 3. The composition according to claim 1 wherein said amphipathic lipid is a phospholipid, including a chemically modified, conjugated or polymerized phospholipid such as pegylated phospholipid.

4. The composition according to claim 1 wherein said phospholipid is selected from the 25 group consisting of phosphatidylcholine, cephalin, isolecithin, phosphatidylethanolamine, distearoylphosphatidylcholine, phosphatidylserine, phosphatidylglycerol, phosphatidic acid, phosphatidylinositol, sphingomyelin, dimyristoylphosphatidylcholine, dimyristoylphosphatidylglycerol, pegylated phospholipids and mixtures, thereof.

30 5. The composition according to claim 4 wherein said amphipathic lipid layer further comprises about 0.05% to about 25% by weight of a steroidal component.

6. The composition according to claim 5 wherein said steroidal component is selected from the group consisting of cholesterol, pegylated cholesterol, coprostanol, cholestanol,

cholestane, C₁ to C₂₄ steroid esters and mixtures, thereof.

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7. The composition according to claim 1 wherein said bioactive agent is selected from the group consisting of anesthetics, systemic antibiotics, antiparasitics, systemic quinolones, anti-infectives, anti-inflammatories, aminoglycosides, cephalosporins, penicillins, antidotes, anti-cholinesterases, metal poisoning antidotes, antineoplastics, 5'-fluorouracil, cytotoxic agents, hormones, steroids, immunomodulators, cytokines, systemic antivirals, systemic antifungals, biologicals, alpha-antitrypsin, bone metabolism regulators, hypercalcemic agent, cardiovascular agents, beta blockers, cerebral vasodilators, cerebral metabolic enhancers, cholinesterase inhibitors, colony stimulating factors, granulocyte-colony stimulating factors, granulocyte macrophage-colony stimulating factors, vasopressors, local diabetic agents, diagnostics such as CT scan enhancers and angiography agents, adenosine deaminase deficiency agents, gonadotropin inhibitors, adrenal cortical steroid inhibitors, gonadotropin releasing hormone stimulant, urofollitropins, muscle relaxants such as neuromuscular blocking agents, prostaglandin analogs, prostaglandins, prostaglandin inhibitors, respiratory therapy agents, anticholinergics, beta andrenergic stimulators, sympathomimetics, and thrombolytics, antithrombotics, anticoagulants, antibiotics antiplatelet agents, thrombolytics, antiproliferatives, steroid and nonsteroidal antiinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration agents, clonidine, estradiol, nicotine, nitroglycerin, and scopolamine steroid and nonsteroidal antiinflammatory drugs, antibacterials, antiprotozoals, 25 antifungals (e.g., nystatin); coronary vasodilators (e.g., nitroglycerin); calcium channel blockers (e.g., nifedipine, diltiazem); bronchodilators (e.g., theophylline, pirbuterol, salmeterol, isoproterenol); enzyme inhibitors such as collagenase inhibitors, protease inhibitors, elastase inhibitors, lipoxygenase inhibitors and angiotensin converting enzyme inhibitors (e.g., captopril, lisinopril); other antihypertensives (e.g., propranolol); leukotriene antagonists (e.g., ICI 204,219); anti-ulceratives such as H2 antagonists; 30 steroid hormones (e.g., progesterone, testosterone, estradiol, levonorgestrel); antivirals and/or immunomodulators (e.g., 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinoline-4-amine, and other compounds disclosed in U.S. Pat. No. 4,689,338, incorporated herein by reference, acyclovir); local

anesthetics (e.g., benzocaine, propofol); cardiotonics (e.g., digitalis, digoxin); antitussives (e.g., codeine, dextromethorphan); antihistamines (e.g., diphenhydramine, chlorpheniramine, terfenadine); narcotic analgesics (e.g., morphine, fentanyl); peptide hormones (e.g., human or animal growth hormones, LHRH); cardioactive products such as atriopeptides; proteinaceous products (e.g., insulin); enzymes (e.g., anti-plaque enzymes, lysozyme, dextranase); antinauseants (e.g., scopolamine); anticonvulsants (e.g., carbamazepine); immunosuppressives (e.g., cyclosporine); psychotherapeutics (e.g., diazepam); sedatives (e.g., phenobarbital); hypnotics; anticoagulants (e.g., heparin); analgesics (e.g., acetaminophen); antimigraine agents (e.g., ergotamine, melatonin, sumatriptan); antiarrhythmic agents (e.g., flecainide); antiemetics (e.g., metaclopramide, ondansetron); anticancer agents (e.g., methotrexate); neurologic agents such as anxiolytic drugs; hemostatics; anti-obesity agents; antigout agents; antianxiety agents; antiinflammatory agents; hormones; immunosuppressive agents; hypolipedemic agents; antiparkinson agents; antifungal agents; analgesics; antimanic agents; antipyretics; antiarthritic agents; antiplatelet agents; anticonvulsants; antidiabetic agents, anticoagulants, antiarrhythmics, antianginal agents; and the like, as well as pharmaceutically acceptable salts, esters, solvates and clathrates thereof.

8. The composition according to claim 1 wherein said lipidized polymer is a lipidized protein.
9. The composition according to claim 8 wherein said protein is selected from the group consisting of enzymes, cell surface proteins, hormones, antibodies, growth factors, clotting factors, neuroproteins, tumor suppressors, toxins, antigens and epitopes of antigens, apolipoproteins, endogenous or exogenous tumor antigenic proteins, bioinvasive molecules (like bacterial invasins), lectins, lectin-like molecules, bacterial toxins such as cholera and macromolecules with bioadhesive properties.
10. The composition according to claim 8 wherein said protein is selected from immunoglobulins, epitopes, transferrin, avidin, hormones, enzymes, integrin, apolipoprotein E, apolipoprotein B100, and mixtures, thereof.
11. The composition according to claim 8 wherein said protein is lysozyme, avidin, apolipoprotein B100 or apolipoprotein E.

12. The composition according to claim 1 wherein said lipid core comprises a mono-, di- or triglyceride.

5 13. The composition according to claim 10 wherein said lipid core comprises triglycerides.

14. The composition according to claim 10 or 11 wherein said mono-, di- or triglyceride is obtained by esterifying glycerol with a fatty acid selected from the group consisting of palmitic, stearic, oleic, linoleic, linolenic and mixtures, thereof.

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15. The composition according to claim 12 wherein said triglyceride is triolein.

16. The composition according to claim 1 wherein said triglycerides are vegetable oils selected from the group consisting of linseed oil, iticica oil, tung oil, soybean oil, sunflower oil, safflower oil, palm oil, poppy seed oil, corn oil, sesame seed oil, olive oil, canola oil, cottonseed oil, castor oil, coconut oil and mixtures, thereof.

20 17. The composition according to claim 1 wherein said bioactive agent is boronated cholesterol.

25 18. A method of enhancing the bioavailability of a bioactive agent in a patient comprising administering to said patient a composition comprising:

i. a microemulsion comprising a lipid core and an amphipathic lipid layer surrounding said lipid core, wherein a hydrophobic portion of said amphipathic lipid layer is associated with said lipid core and a hydrophilic portion of said amphipathic lipid layer is associated with a hydrophilic surface of said amphipathic lipid;

ii. a bioactive agent; and

iii. optionally, a lipidized polymer;

30 said bioactive agent being included in said composition in an effective amount, said amphipathic lipid being included in said composition in an amount effective to form a microemulsion with said lipid core, and said lipidized polymer being included in said composition in association with said amphipathic lipid in an amount ranging from about 0.01% to about 65% by weight of said composition.

19. The method according to claim 18 wherein said lipidized polymer is a lipidized targeting protein and said bioavailability of said bioactive agent is enhanced in one or more tissues of said patient.

5 20. The method according to claim 19 wherein said targeting protein is selected from the group consisting of immunoglobulins, immunogens, transferrin, avidin, lysozyme, hormones, enzymes, integrin, monoclonal antibodies and mixtures, thereof.

10 21. The method according to claim 18 wherein said lipidized polymer is lysozyme, avidin or polylysine.

22. A method of enhancing the bioavailability of a bioactive agent to a predetermined site or tissue within a patient comprising administering to said patient a composition comprising:

i. a microemulsion comprising a lipid core and an amphipathic lipid layer

15 surrounding said lipid core, wherein a hydrophobic portion of said amphipathic lipid layer is associated with said lipid core and a hydrophilic portion of said amphipathic lipid layer is associated with a hydrophilic surface of said amphipathic lipid;

ii. a bioactive agent; and

iii. a lipidized polymer;

20 said bioactive agent being included in said composition in an effective amount, said amphipathic lipid being included in said composition in an amount effective to form a microemulsion with said lipid core, and said lipidized polymer is a lipidized targeting protein included in said composition in association with said amphipathic lipid in an amount ranging from about 0.01% to about 65% by weight of said composition.

25 23. The method according to claim 18 wherein said lipidized targeting protein is selected from the group consisting of immunoglobulins, immunogens, transferrin, avidin, lysozyme, hormones, enzymes, integrin, monoclonal antibodies and mixtures, thereof.

30 24. The method according to claim 19 wherein said targeting protein is lysozyme or avidin.

25 25. A method of enhancing the stability of a microemulsion, said microemulsion comprising a lipid core and an amphipathic lipid layer surrounding said lipid core, wherein a hydrophobic portion of said amphipathic lipid layer is associated with said lipid core and a

hydrophilic portion of said amphipathic lipid layer is associated with a hydrophilic surface of said amphipathic lipid and a bioactive agent, said method comprising incorporating within said microemulsion an amount of a lipidized polymer effective to enhance stability of said microemulsion, said bioactive agent being included in said composition in an effective amount, said amphipathic lipid being included in said composition in an amount effective to form a microemulsion with said lipid core, and said lipidized polymer is included in said composition in association with said amphipathic lipid in an amount ranging from about 0.01% to about 65% by weight of said composition.

10 26. The method according to claim 25 wherein said lipidized polymer is a lipidized targeting protein and said bioavailability of said bioactive agent is enhanced in one or more tissues of said patient.

15 27. The method according to claim 26 wherein said targeting protein is selected from the group consisting of immunoglobulins, immunogens, transferrin, avidin, lysozyme, hormones, enzymes, integrin, monoclonal antibodies and mixtures, thereof.

20 28. The method according to claim 25 wherein said lipidized polymer is lysozyme, avidin or polylysine.

25 29. A method of transferring a bioactive agent from a microemulsion to a natural lipoprotein *in vitro*, said method comprising formulating a microemulsion in combination with a bioactive agent and incubating said microemulsion and bioactive agent in the presence of a natural lipoprotein and a lipid transferring protein at a temperature and for a time effective to produce transfer of said bioactive agent from said microemulsion to said natural lipoprotein.

30 30. The method according to claim 28 wherein said natural lipoprotein is selected from the group consisting of LDL, VLDL, IDL, HDL and chylomicrons.

31. The method according to claim 29 wherein said natural lipoprotein is LDL.

32. The method according to claim 28 wherein said bioactive agent is BCH.

33. A pharmaceutical composition comprising:

- i. a microemulsion comprising a lipid core and an amphipathic lipid layer surrounding said lipid core, wherein a hydrophobic portion of said amphipathic lipid layer is associated with said lipid core and a hydrophilic portion of said amphipathic lipid layer is associated with a hydrophilic surface of said amphipathic lipid;
- ii. an effective amount of a bioactive agent selected from the group consisting of cholesterol 1,12-dicarba-closo-dodecaborane 1-carboxylate, cholesterol 1,2-dicarba-closo-dodecaborane 1-carboxylate, cholesterol 1,7-dicarba-closo-dodecaborane 1-carboxylate and mixtures, thereof; and

ii. optionally, a lipidized polymer;

bioactive agent being included in said composition in an effective amount, said amphipathic lipid being included in said composition in an amount effective to form a microemulsion with said lipid core, and said lipidized polymer being included in said composition in association with said amphipathic lipid in an amount ranging from about 5% to about 65% by weight of said composition.